REMARKS

Status of the claims

Claims 1-5, 22-28 and 30-55 were previously pending. Claims 1, 3, 5, 23, 24, 33-35, 38 and 42-52 have been withdrawn from consideration as a result of restriction and species election requirements dated July 1, 2004 and October 28, 2004.

By virtue of the present response, claims 32, 41, 52 and 53 are amended, without prejudice or disclaimer, and new claims 56-61 are added. Support for claims 56-60 is found, for example, at page 8, lines 11-14 and Examples 2, 3 and 7. Support for claim 61 is found in a previous version of claim 30 (see Response dated May 19, 2005).

Accordingly, claims 1-5, 22-28 and 30-61 are pending and claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-61 are under consideration.

Restriction

Applicants reiterate their argument, presented in a response dated May 19, 2005, that claim 30 (of Group II) is a linking claim, linking the proteins of Group I (which are encoded by the polynucleotide of claim 30) with the methods of Group III (which utilize the polynucleotide of claim 30). The arguments presented in the Office Action dated November 15, 2005, to the effect that claim 30 is not a linking claim, are traversed inasmuch as the isolated polynucleotide of claim 30 both encodes the proteins of Group I and is used in the methods of Group III. Moreover, method claims 42-51 (Group III) contain all of the limitations of claim 30, and should be rejoined and examined upon allowance of claim 30.

Finally, Applicants note that, with respect to engineered zinc finger proteins, the Office has previously determined that concurrent search and examination of nucleic acids and proteins does not impose a serious burden. *See* co-owned application serial No. 10/651,761 Decision on Petition dated March 30, 2005. Accordingly, Groups I and II should be rejoined.

Interview

The undersigned thanks Examiner Dunston and Supervisory Examiner Qian for participating in a personal interview on July 19, 2006 at which the outstanding rejections, and possible approaches for overcoming the rejections, were discussed. Applicants agree with the substance of the interview as set forth in the Examiner's Interview Summary dated July 19, 2006.

35 U.S.C. § 101

Claims 32 and 41 stand rejected as allegedly directed to non-statutory subject matter. Office Action at page 3. In response, claims 32 and 41 have been amended to recite an isolated host cell. Support for the amendment is found, *e.g.*, in Example 3 (*esp.* at page 47) and Example 8. Accordingly, the rejection can be withdrawn.

35 U.S.C. § 112, first paragraph

Written description

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-55 stand rejected under 35 U.S. C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action at pages 4-8. The Office Action acknowledges that cysteine and histidine residues (as recited in independent claims 30 and 58-60) are known to coordinate a zinc atom in a zinc finger, but cites Green for the proposition that the zinc coordinating cysteine and histidine residues are not predictably interchanged, because conversion of finger 2 alone, or combinations of fingers 1 and 3 or fingers 2 and 3, of Zif268 to a C_4 finger abolish DNA binding.

Applicants traverse the rejection and supporting remarks. As previously stated,[1] all members of the genera embodied by the pending claims are clearly and adequately described. Indeed, the Office acknowledges that the skilled artisan can clearly envision the proteins encoded by the claimed nucleic acids and that the relevant sequences of all

[1] Response dated December 5, 2005 at pages 2-4

claimed species have been disclosed. For example, in the Office Action dated December 23, 2005, at page 5, the Examiner states:

> . . . one of skill in the art could envision every single amino acid change to the primary amino acid sequence represented by the formulas within the specification and claims.

Given that the Office agrees that all claimed species are adequately described, the written description rejection appears to be based on the contention that not every substitution of a zinc coordinating residue will result in adoption of a ββα structure, or will generate a protein capable of binding DNA. However, such contentions do not provide sufficient basis to support a written description rejection.

Moreover, Applicants note that polynucleotides encoding proteins that do not adopt a ββα structure, and polynucleotides encoding proteins that do not bind DNA, are not encompassed by the claims (see, *e.g.*, claims 30, 58 and 61). In using such contentions as the basis for a rejection, the Examiner is improperly reading structural and functional limitations out of these claims.

With regard to claims 59 and 60, adoption of a ββα structure is not recited and therefore the ability of a protein, covered by these claims, to adopt such a conformation is immaterial to their written description.

Thus, when properly construed with all limitations considered, the claims are adequately described, as set forth above and acknowledged by the Office. Accordingly, the rejection should be withdrawn.

Enablement

Claim 53 was rejected as allegedly not enabled, based essentially on the alleged unpredictability of gene therapy. Office Action at pages 8-11. In response, claim 53 has been amended to remove the word "pharmaceutical." Accordingly, this rejection can be withdrawn. Withdrawn claim 52 has been similarly amended.

35 U.S.C. § 102

Claims 2, 4, 26-28, 30-32 and 54 stand rejected as allegedly anticipated by Green. Office Action at pages 13-15. Green discloses construction of mutants of zif268 in which each of the three constituent zinc fingers was converted from its naturally-occurring C_2H_2 (CCHH) configuration to a C_4 (CCCC) configuration. Green also constructed mutants of zif268 in which both fingers 1 and 3, and fingers 2 and 3, were converted to the C_4 configuration. The Office states that Green discloses polynucleotides encoding mutated zif268 proteins in which, in the first or third finger, one of the C-terminal zinc-coordinating residues is a cysteine, and that these mutated zif268 proteins were engineered to bind to the wild-type zif268 target sequence. The Office also states that Green provides indirect evidence that his mutated zif268 proteins adopted a ββα structure, based on their ability to bind DNA. Office Action at paragraph bridging pages 13-14.[2]

Applicants traverse the rejection and supporting remarks, for the following reasons.

Independent claim 30 and new claims 58-61 require that the claimed polynucleotides encode proteins that are "engineered to bind to a target sequence." See part (ii) of claims 30, 58, 59 and 60, and part (iii) of claim 61. This limitation must be considered in construing the claim in light of the prior art. See, *e.g.*, *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 72 USPQ2d 1001, 1007 (Fed. Cir. 2004) ("While not an absolute rule, all claim terms are presumed to have meaning in a claim") and *Glaxo, Inc. v. Novopharm, Ltd.*, 42 USPQ2d 1257, 1263 (Fed. Cir. 1997) ("It is elementary patent law that all [claim] limitations are material.").

In the instant application, the meaning of the claim term "engineered" is provided at page 10, lines 17-29 of the specification, indicating that a zinc finger protein can be

[2] Applicants assume that the references to "Chen et al" on page 14 of the Office Action actually denote the Green et al. reference, as no "Chen et al." reference is listed on any PTO-892 or Information Disclosure Statement present in Applicants' copy of the file, and Green et al. is the only reference cited in the § 102 rejection. If this assumption is incorrect, clarification is requested.

engineered to bind a target sequence using design methods (based on rational criteria) or empirical selection processes such as phage display.[3]

Moreover, claims must be construed from the point of view of one skilled in the art to which the invention pertains. Indeed, the importance of construing claim language in light of the art was recently reaffirmed by the Federal Circuit, *en banc*, in *Phillips v. AWH*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005). Therein, the court, citing a number of previous decisions,[4] confirmed its precedent that claim terms are given their ordinary and customary meaning to a person of ordinary skill in the art at the effective filing date of the patent application:

> We have made clear, moreover, that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.[5]

The effective filing date of the application providing support for the claimed subject matter is January 22, 2001. At that date, skilled artisans were aware that the term "engineered zinc finger protein" referred to non-naturally-occurring zinc finger proteins having a binding specificity different from that of any naturally-occurring zinc finger protein, said binding specificity having been determined by the investigator, using empirical selection methods or rational design methods. See, for example, U.S. Patent No. 5,789,538 (Issued August 4, 1998; Reference A26 of IDS mailed on May 9, 2005) at column 8, lines 21-28:

> Based on the present disclosure, the skilled artisan will be able to select a wide variety [of] four base pair sequences and engineer zinc fingers which bind specifically to desired four base pair sequence[s]. . . . As a result, a multifingered

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[3] Applicants note that all references cited in this portion of the specification have been made of record, in Information Disclosure Statements mailed on April 11, 2003 (considered by Examiner McKelvey on February 7, 2005) and on May 9, 2005 (considered by Examiner McKelvey on November 12, 2005)

[4] See, for example, *Vitronics Corp. v. Conceptronic, Inc.* 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Ferguson Beauregard/Logic Controls v. Mega Sys., LLC*, 350 F.3d 1327, 1338 (Fed. Cir. 2003) and *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004)

[5] *Phillips v. AWH Corp.*, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005)

> protein can be engineered such that each finger binds to an adjacent and overlapping subsite.

See also U.S. Patent No. 6,013,453 (Issued January 11, 2000; Reference A3 of IDS mailed on April 11, 2003) at column 2, lines 48-54:

> Protein engineering experiments have shown that it is possible to alter rationally the DNA-binding characteristics of individual zinc fingers when one or more of the α-helical positions is varied in a number of proteins [references omitted].

See also WO 00/41566 (published July 20, 2000; Reference B20 of IDS mailed on May 9, 2005) at page 22, lines 14-15:

> The ZFPs [zinc finger proteins] of the invention are engineered to recognize a selected target site in the endogenous gene of choice.

These and other references, which were available on the priority date of the subject application, show that one of skill in the art would have understood the term "engineered zinc finger protein" to denote a non-naturally-occurring protein whose amino acid sequence had been altered to enable it to bind to a target nucleotide sequence of choice. Thus, the Examiner must, according to *Phillips*, give patentable weight to the limitation that the claimed polynucleotides encode engineered zinc finger proteins obtained using design methods (based on rational criteria) or empirical selection processes such as phage display.

Taking the foregoing into account, it is clear that the mutated zif268 proteins disclosed by Green are not engineered to bind a target sequence. No rational design rules or empirical selection methods were used in their construction. Rather, Green simply used a known, naturally-occurring protein that bound a known target sequence, altered certain zinc-coordinating residues, and tested the mutant proteins for their ability to bind to the same target sequence. In rejecting the claims based on Green, the Examiner has again improperly neglected to consider all of the limitations of the claims, by reading out the limitation that the proteins encoded by the claimed polynucleotides are engineered to

bind a target sequence. When the claims are properly construed and this limitation is taken into account, it is clear the Green fails to disclose the claimed polynucleotides.

Finally, Green fails to anticipate new claims 58 and 60 for the additional reason that these claims do not encompass zinc fingers in which all four zinc coordinating residues are cysteines.

For all of the foregoing reasons, the rejection is improper and should be withdrawn.

35 U.S.C. § 103

A. Claims 25, 36 and 39-41 stand rejected as allegedly obvious over Green in view of Pomerantz (Office Action at pages 15-17). Green is cited as above and Pomerantz is stated to disclose design of a polynucleotide encoding an artificial transcription factor DNA binding domain fused to a VP16 transcriptional activation domain. *Id.* Pomerantz is also stated to disclose *in vivo* assays of his artificial transcription factor in which binding to promoter sequences was assayed. *Id.*

Applicants traverse the rejection and supporting remarks.

As noted above, Green fails to disclose or suggest the claimed polynucleotides encoding zinc finger proteins that are engineered to bind to a target sequence. Pomerantz fails to cure this deficiency, disclosing only two naturally-occurring, C_2H_2 zinc fingers from zif268 fused to a naturally-occurring Oct-1 homeodomain. Thus, Pomerantz's fusion protein is, first of all, not a zinc finger binding protein, as claimed, since it also contains a homeodomain. Secondly, the zinc finger portion of Pomerantz's protein is not engineered to bind a target sequence, consisting merely of two naturally-occurring zinc fingers from zif268. Thus, neither Green nor Pomerantz disclose or suggest zinc finger proteins that are engineered to bind to a target sequence; accordingly, their combination also fails to disclose or suggest engineered zinc finger proteins. For these reasons, the rejection is improper and should be withdrawn.

B. Claims 22 and 37 stand rejected as allegedly obvious over Green in view of Pomerantz and further in view of Guyer. (Office Action at pages 17-19). Green and

Pomerantz are applied as above, and Guyer is cited as disclosing plant cells and a plant C1 activation domain.

Applicants traverse the rejection and supporting remarks. As discussed above, Green and Pomerantz, taken together, fail to make the claimed subject matter obvious, and Guyer adds nothing to cure the deficiencies of those references.

C. Claims 25, 36, 39-41 and 55 stand rejected as allegedly obvious over Green in view of Barbas (Office Action at pages 19-21). Green is applied as above. Barbas is stated to disclose "expanded" zinc finger proteins to which additional fingers have been added, mutagenized expanded zinc finger proteins, expanded zinc finger proteins fused to dimerizaton domains and activation domains, and activation of transcription from a promoter.

Applicants traverse the rejection and supporting remarks.

As noted above, Green fails to disclose or suggest the claimed polynucleotides encoding zinc finger proteins that are engineered to bind to a target sequence. Barbas, for its part, discloses only C_2H_2 zinc finger proteins (see, for example, independent claims 1, 14, 22, 28 and 49 of Barbas) Being so limited, Barbas teaches away from combining his disclosure with that of Green's C_4 zinc finger protein, or indeed with the disclosure of any non-C_2H_2 zinc finger protein. For these reasons, there is no motivation to combine the disclosures of Green and Barbas. Accordingly, the rejection should be withdrawn.

CONCLUSION

In light of the amendments and remarks presented herein, it is believed that the elected subject matter is in condition for allowance. Applicants therefore request examination of generic subject matter. If the Examiner believes that a telephone conversation would expedite prosecution, she is invited to contact the undersigned at the telephone number given below.

Respectfully submitted,

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